Benzo[*b*]thiophene Derivatives. XXVII. 5-Methoxy-6-halo-3-β-acetamidoethylbenzo[*b*]thiophenes, Blocked Analogs of Melatonin [1]

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The preparation of the 6-fluoro and 6-chloro analogs of the title compound is described, in a seven-step synthesis giving 30-40% overall yields. All intermediates have been isolated and characterized, including important by-products, such as the corresponding benzo[*b*]thienyl-3-acetic acids, and 3-methylbenzo[*b*]thiophenes. Cyclization of the 3-halo-4-methoxyphenylthioacetoacetic esters gave more *ortho*-cyclization in the chlorine case than was observed for the fluorine derivative. The title compounds were shown to have weak antiovulatory action, with the fluoro analog most active.

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In a recent paper [2] we called attention to the possible advantages of sulfur analogs of melatonin bearing a blocking group at the 6-position, *e.g.* the 5-methoxy-6-halo-3-*b*-acetamidoethylbenzo[*b*]thiophenes, as potential anti-ovulatory agents. Earlier studies on the metabolism of biologically active benzo[*b*]thiophenes [3,4] have shown that the major pathway of metabolism of the benzo[*b*]thiophene ring involves 6-hydroxylation, with no evidence of thiophene ring degradation. This contrasts to melatonin metabolism, which is very rapid, and in which pyrrole ring oxidation provides a fascile alternate pathway [5]. Thus a sulfur analog of melatonin, bearing a fluorine or chlorine at position-6 should be metabolized more slowly, and exhibit longer duration of activity.

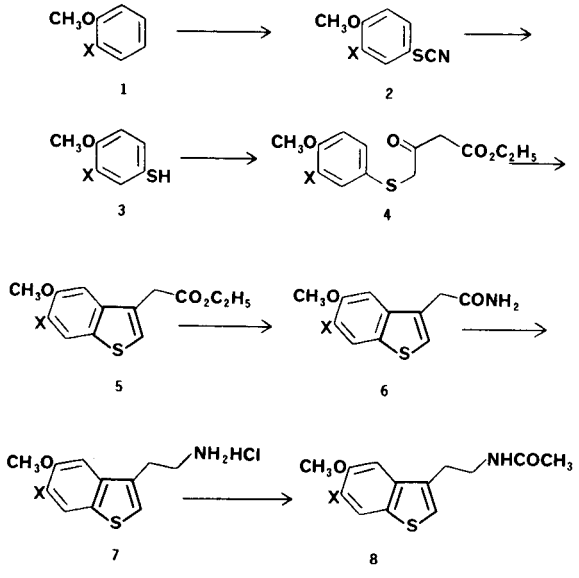
The synthesis of a variety of melatonin analogs was recently undertaken with the intention of producing compounds with similar physiological properties but greater resistance to metabolism [5]. Particular emphasis was placed on melatonin derivatives having a fluorine of chlorine atom blocking the 6-position, compounds which showed enhanced activity in inhibiting ovulation in rats. The assumption that these compounds would be more slowly metabolized than melatonin was born out by the prolonged serum half-life of 6-chloromelatonin, which was found to be 27 minutes, following intravenous administration, in contrast to 12-15 minutes reported for melatonin. The sulfur analog of melatonin, 5-methoxyl-3-β-acetamidoethylbenzo[*b*]thiophene (**8**, Scheme 1, X = H) has similar activity to melatonin [6], and was shown to be more lipid soluble than melatonin, with longer half-life in plasma and all tissues [7]. We therefore undertook the synthesis of the sulfur analogs of melatonin, bearing a halogen at the 6-position (**8a** and **8b**, Scheme 1) to examine their activity as antiovulatory agents.

Our earlier paper [2] reported the synthesis of 5-methoxy-6-chloro-3-β-acetamidoethylbenzo[*b*]thiophene (**8b**) in a 13 step synthesis from commercially available *m*-hydroxyacetophenone in about 1.5% overall yield. We report here an alternate synthetic scheme (Scheme 1) to synthesize 5-methoxy-6-fluoro-3-β-acetamidoethylbenzyl[*b*]-thiophene (**8a**), which resulted in an overall yield of about 40% in 7 steps from commercially available *o*-fluoroanisole. The synthesis of **8b** was then attempted by this scheme, starting with *o*-chloroanisole, and, although the reactions were not as clean with the chloro analog as they had been with the fluoro sequence, an overall yield of about 29% of **8b** was obtained. This method, which involves cyclization of 4-arylthioacetoacetic esters has proved useful in the synthesis of a variety of 5,6-disubstituted benzo[*b*]thiophene-3-acetic acid derivatives, having electron-releasing groups (*e.g.* hydroxy, methoxy or methyl) at the 5- and 6-positions [6]. However, studies on *p*-methoxyphenylthioacetoacetic ester gave very poor yields of 5-methoxybenzo[*b*]thiophene-3-acetic acid and much polymeric material under these cyclizing conditions [8]. It was therefore interesting to examine this ring-closure in cases having a halogen *para* to the site of ring-closure, and a methoxy group *meta* to this site.

Thiocyanation of *o*-fluoroanisole (**1a**) gave 3-fluoro-4-methoxyphenylisothiocyanate (**2a**) in good yield. Assignment of structure **2a** is based on nmr spectral data. A slightly distorted doublet at 7.32 ppm for two protons is caused by overlapping of two doublets, one for H-2, split by the *ortho*-fluorine atom, and one for H-6, split by the proton at H-5 (JH-F = 10 to 11 ppm, J *ortho* H-H = 10). A triplet at 7.01 for one proton corresponds to H-5, split by H-6 and the *meta*-fluorine atom. Structure **2a** is the only possible structure consistent with this data. Reduction of **2a** under nitrogen gave the thiol **3a**, an oil which was converted to the corresponding disulfide for characterization. Reaction of **3a** with ethyl 4-chloroacetoacetate gave a nearly quantitative yield of crude β-ketoester **4a**. An attempt to purify this oil by distillation failed, due to decomposition, but ir and nmr spectral data were satisfactory for

structure **4a**.

Scheme 1

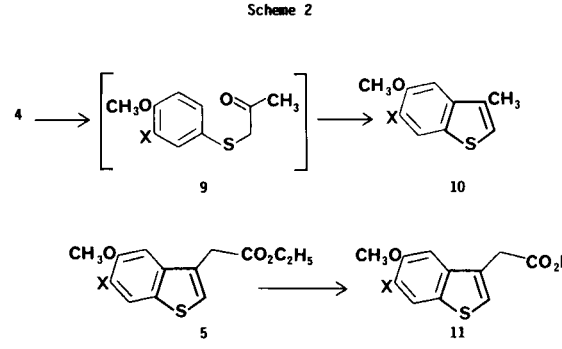


a) X = F, b) X = Cl

Cyclization of crude **4a** was accomplished using a heterogeneous acid catalyst, prepared by mixing polyphosphoric acid, phosphorus pentoxide and celite in such a way as to form a fine granular product. When this material was refluxed with dry toluene, and **4a** in toluene added, a satisfactory yield of **5a** was obtained. The bath temperature in this reaction must be carefully controlled, and fresh phosphorus pentoxide used, to reduce some hydrolysis of the esters present, which always occurs. Work up of the toluene layer included a bicarbonate wash, and acidification of this extract precipitated a small amount of 6-fluoro-5-methoxybenzo[*b*]thienyl-3-acetic acid (compound **11a**, Scheme 2). Ester **5a** is an oil, which was purified on a silica gel column. The first fraction off the column was found to contain a small amount of 5-methoxy-6-fluoro-3-methylbenzo[*b*]thiophene (compound **10a**, Scheme 2). These two impurities can only have arisen by hydrolysis of two esters present in the cyclization reaction. Compound **10a** must be formed by cyclization of 4-methoxy-3-fluorophenylthioacetone (**9a**) which was formed by hydrolysis and decarboxylation of **4a** during the reaction. Compound **11a** obviously is formed by hydrolysis of ester **5a**. These reactions are shown in Scheme 2. There was no evidence of cyclization occurring *ortho* to the fluorine atom in any of the isolated products.

The structure of **5a** was supported by the nmr spectrum, showing three isolated aromatic protons H-2, H-4, and H-7, the latter split by the *ortho*-fluorine atom. Amide **6a**

Scheme 2



a) X = F, b) X = Cl

was obtained in good yield by treating the ester **5a** with ammonia in ethylene glycol, and this amide reduced by the method of Brown [9] to form the hydrochloride **7a**. The crude hydrochloride was contaminated with some water-insoluble material, probably a borate complex, which was easily removed by solution of the crude hydrochloride in water, filtering and acetylating the amine in aqueous basic solution to give **8a** in excellent yield.

We therefore turned our attention to a resynthesis of compound **8b**, the 6-chloro analog previously reported [2]. The first three reactions shown in Scheme 1 were nearly quantitative. Thiocyanation of *o*-chloroanisole (**1b**) using about 1.5 equivalents of thiocyanogen chloride in acetic acid, gave a nearly quantitative yield of **2b**, a low-melting solid whose nmr showed quite clearly the ABX aromatic pattern expected. Reduction of **2b** with lithium aluminum hydride gave (**3b**) in high yield, and condensation with 4-chloroacetoacetate in pyridine/ether solution gave the ester **4b** in 100% yield.

The ester **4b** was used as isolated in the cyclization step, although it could be purified with considerable loss on a silica-gel column. The polyphosphoric acid cyclization step caused some difficulties. As had been noted in the case of the fluoro analog, some hydrolysis of the ester occurred both before and after cyclization. In addition, we found some evidence of cyclization occurring *ortho* to the chlorine atome (about 12-18%). These products were probably magnified by the fact the cyclization was much slower for the chloro compound than had been required for the fluoro analog, which cyclized quite cleanly in four hours. It was necessary to run the cyclization of the chloro analog in refluxing toluene for twenty-four hours to obtain a reasonable yield. The crude oil so obtained was largely the desired ester **5b**, as shown by chromatography. However, it also contained some 5-methoxy-6-chloro-3-benzo[*b*]thienylacetic acid (**11b**) which could be recovered from the alkaline washings of the toluene solution. Its structure was confirmed by comparison to an authentic sample obtained

Table I

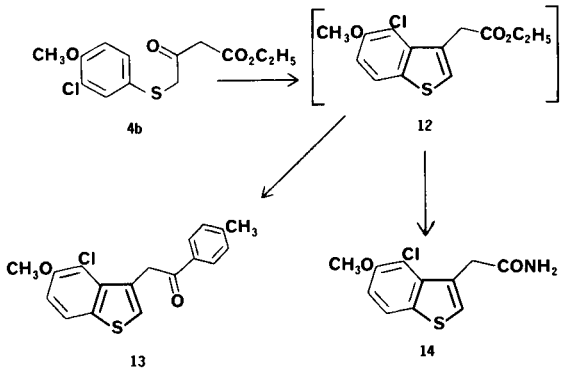
Anti-ovulatory Evaluation of Sulfur Analogs of Melatonin

Compound	Dose (mg) [a]	Treatment [b] volume per injection (ml)	No. Animals [c] ovulating	No. Eggs [d] recovered
8 (X = H)	12	0.3	3/10	27
	control	0.3	10/10	127
	24	0.6	4/10	41
	control	0.6	9/10	110
8a (X = F)	15	0.5	3/10	43
	control	0.5	10/10	117
	30	1.0	1/10	10
	control	1.0	8/10	101
8b (X = Cl)	12	0.3	2/10	25
	control	0.3	9/10	120
	24	0.6	6/10	78
	control	0.6	10/10	112
	30	1.0	5/10	64
	control	1.0	9/10	119

[a] Total dose by subcutaneous injection in 3 equal volumes (10% ethanol in sesame oil) on day of proestrus, at noon, 2:30 and 5:00 PM. [b] When compared to control vehicle, treatment volume indicated in table was very slightly turbid, due to low solubility. A small portion of each compound appeared to be in fine colloidal form. [c] Young female Sprague-Dawley rats, selected for uniform 4-day estrus cycle. Groups of control rats received only vehicle. [d] Rats sacrificed on day of estrus, and oviducts removed and searched for eggs. Total number of eggs from animals ovulating shown.

by hydrolysis of ester **5b**. The initial elution from the column gave nearly 5% of 5-methoxy-6-chloro-3-methylbenzo[*b*]thiophene (**10b**), which must have arisen by hydrolysis and decarboxylation of ester **4b** to form the arylthioacetone **9b**, which was then cyclized to **10b**. The second fraction from the column proved to contain about 52% of ester **5b**, contaminated with some of the *ortho*-cyclized ester **12** (Scheme 3). These two compounds could not be separated by chromatography, but the presence of **12** was detected in the nmr spectrum of the isolated esters. Two doublets, at δ 6.9 (J = 9) and 7.55 (J = 9), equivalent to about 0.1 proton each, clearly showed the presence of *ortho*-hydrogens.

Scheme 3



Two other compounds derived from ester **12** confirmed its presence in the mixture. The final eluent from the column was concentrated to produce a small amount of the ketone **13**, which must arise by acid-catalyzed condensation of ester **12** with toluene. Such condensations are well known [10], but it is difficult to explain why none of the isomeric product, derived from the major ester component of the mixture (**5b**) was observed. The structure of **13** is quite certain, based on molecular weight, elemental analyses and nmr spectral data, which shows a *para*-substituted toluene, with two protons showing a doublet at δ 7.30 (J = 8) and two protons showing a doublet at δ 8.0 (J = 8), and a 3,4,5-trisubstituted benzo[*b*]thiophene with three protons; a singlet for H-2 at δ 7.28, and two doublets, one at δ 7.07 (J = 9) for H-6, and the other at δ 7.72 (J = 9) for H-7. Possibly the *peri*-chlorine in **12** activates the carbonyl group of the ester to Friedel-Crafts acylation.

We had previously observed that the amide **6a** had very low solubility in most common organic solvents. It therefore seemed reasonable to convert the crude ester **5b**, with its various impurities, into amide **6b**, and purify at this stage by recrystallization. Treatment of the crude ester **5b** with ammonia gave an off-white solid which was washed with ether, and then recrystallized from methanol several times to give pure amide **6b**, which was also prepared in high yield from pure **5b** obtained by chromatography of the crude ester. The methanol mother liquors from recrystallizations of **6b** in a series of preparations was collected and concentrated, and the solid recrystallized several times from ethanol to give the isomeric amide, **14**. The structure of **14** was confirmed by the presence of the *ortho*- proton doublets in the nmr.

Reduction of amide **6b** gave the amine hydrochloride **7b** in 90% yield, which was identical to the authentic sample previously reported and acetylation converted this to the known acetamide **8b** [2]. This seven step synthesis gave an overall yield from *o*-chloroanisole of about 29%. Although the cyclization 4-(3′-chloro-4′-methoxyphenylthio)acetoacetic ester (**4b**) is less facile and produces more isomeric products, including *ortho*-cyclization products, than the corresponding cyclization of 4-(3′-fluoro-4′-methoxyphenylthio)acetoacetic ester (**4a**), it was still possible to produce the desired product **8b** in superior yields in only one-half as many steps.

Biological Evaluation.

The melatonin analogs reported here (**8a** and **8b**) plus the unsubstituted sulfur analog of melatonin (**8**, X = H), previously synthesized in this laboratory [11] were submitted to the Center for Population Research, Contraceptive Development Branch, National Institutes of Health, for evaluation of anti-ovulatory activity. The comparative results are shown in Table I [12]. All three of the compounds showed weak anti-ovulatory activity, comparable to that of melatonin itself, which is reported to be active at 8 mg/rat, on single intravenous injection, (1/10 rats ovulated following day) [5]. A like activity is shown by the fluoro-blocked analog (**8a**) at 30 mg/rat by subcutaneous injection (Table I). The chloro-blocked analog (**8b**) is somewhat less active, comparable to the unsubstituted analog (**8**, X = H) (Table I).

It was interesting to determine whether the blocking group did inhibit the metabolism of these sulfur analogs of melatonin. Therefore tests were run in which the animals were treated on diestrus (the day preceding proestrus), using a single large dose (100 mg) of the compound. The unsubstituted compound **8**, (X = H) and the 6-fluoro compound **8a** are compared in Table II. Both compounds are still active when administered on the day of diestrus, but no significant difference in activity is shown in Table II.

Table II

Duration of Anti-ovulatory Activity of Sulfur Analogs of Melatonin

Compound	Dose (mg) [a]	No. animals [b] ovulating	No. eggs recovered
8 (X = H)	100	5/10	71
	control	10/10	129
8a (X = F)	100	4/10	45
	control	10/10	116

[a] Single subcutaneous inject in 0.5 ml of vehicle at noon on day of diestrus. [b] Sprague-Dawley rats, sacrificed 48 hours post-injection.

EXPERIMENTAL

Melting points were determined on a "uni-melt" Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137-B infrared spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian T 60A spectrometer using tetramethylsilane as an internal standard. Mass spectral analyses were performed on a Varian MAT CH7 at 70eV ionization potential. Eastman chromatogram sheets (# 13181 Silica gel with fluorescent indicator # 6060) were used for thin layer chromatography. Elemental analyses were performed by Midwest Microlab, Indianapolis

3-Fluoro-4-methoxyphenylisothiocyanate (**2a**).

A mixture of 475 ml of glacial acetic acid and 25 ml of acetic anhydride was maintained at reflux for 2 hours, then cooled in an ice bath, and 7.8 g (0.11 mole) of chlorine gas added [13]. Then 16.64 g (0.0515 moles) of dry lead thiocyanate was added, with stirring. To this thiocyanogen chloride solution, containing precipitated lead chloride, was added 12.6 g (0.10 mole) of *o*-fluoroanisole (**1a**) (Aldrich). The mixture was stirred at room temperature for 7 hours; the lead chloride was then collected, and 3 liters of water added to the filtrate. After storing overnight in a refrigerator, the precipitate was collected, dried, and recrystallized from carbon tetrachloride to give 14.1 g (77%) of colorless needles (caution, irritant) of **2a**, melting at 48-49°: ir (potassium bromide): 2160 cm^{-1} (CN); nmr (deuteriochloroform): δ 3.42 (s, 3H, CH_3), 7.01 (t, 1H, H-5), 7.32 (q, 2H, H-2 and H-6).

Anal. Calcd. for C_8H_6FNOS: C, 52.46; H, 3.28; N, 7.65; S, 17.49; F, 10.38. Found: C, 52.35; H, 3.27; N,7.80; S, 17.53; F, 10.60.

3-Fluoro-4-methoxybenzenethiol (**3a**).

A solution of 18.3 g (0.10 mole) of **2a** in 90 ml of dry ether was added dropwise to 4.9 g (0.13 mole) of LAH suspended in 400 ml of dry ether in a three-necked flask under a nitrogen atmosphere. When addition was complete the mixture was refluxed for 2 hours, then quenched by dropwise addition of water, followed by 6*N*-hydrochloric acid until inorganic salts were dissolved. The ether layer was separated, and the water layer washed twice with ether. The combined ether layers were washed once more with water, and dried (magnesium sulfate). Removal of ether gave 15.3 g (96.8%) of yellow oil. Distillation under reduced pressure gave 14.7 g (93%) of pale yellow oil boiling at 42.5° (0.1 mm); ir (neat): 2560 cm^{-1} (SH); nmr (deuteriochloroform): δ 3.43 (s, 1H, SH), 3.87 (s, 3H, CH_3), 6.82 (t, 1H, H-5), 7.1 (d, 2H, H-2, H-6).

Anal. Calcd. for C_7H_7FOS: C, 53.16; H, 4.43; S, 20.25; F, 12.03. Found: C, 52.96; H, 4.29; S, 20.20; F, 12.12

3-Fluoro-4-methoxyphenyl Disulfide.

About 0.6 g of **3a** was dissolved in 5 ml of ethanol, to which one drop of 4*M* sodium hydroxide solution had been added. Then a solution of iodine in ethanol was added dropwise with stirring until the iodine color persisted. The mixture was cooled in an ice-bath, filtered, and the precipitate washed with dilute sodium bisulfite solution, then water. After drying, the white solid was recrystallized from carbon tetrachloride/hexane mixture to give colorless crystals melting at 74-75°; nmr (deuteriochloroform): δ 3.87 (s, 3H, CH_3), 6.87 (t, 1H, H-5), 7.2 (m, 2H, H-2 + H-6).

Anal. Calcd. for $C_{14}H_{12}F_2O_2S_2$: C, 53.50; H, 3.82; S, 20.38; F, 12.10. Found: C, 53.78; H,3.78; S, 19.91; F, 12.51.

Ethyl 3-Fluoro-4-methoxyphenylthioacetoacetate (**4a**).

To a solution of 7.9 g (0.05 mole) of **3a** and 20 g of pyridine in 30 ml of dry ether was added 9.24 (0.055 mole) of 98% ethyl 4-chloroacetoacetate (Aldrich) with stirring. A white precipitate formed immediately. After 2 hour reflux, 70 ml of water was added, and the ether layer separated. The aqueous layer was extracted twice with ether, and the combined ether extracts washed with water, then 3*N* hydrochloric acid, and finally brine, and dried (magnesium sulfate). Concentration of the ether solution gave 13.7 g (95.8%) of an oil. Attempts to distill this oil caused charring, so it was used in the next step without further purification; ir (neat): 1735 (ester CO), 1690 cm^{-1} (ketone CO); nmr (deuteriochloroform): δ 1.26 (t, 3H, CH_3), 3.6 (s, 2H, CH_2), 3.75 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.2 (q, 2H, CH_2), 6.9 (t, 1H, H-5), 7.2 (d, 2H, H-2 + H-6).

Ethyl 5-Methoxy-6-fluoro-3-benzo[*b*]thienylacetate (**5a**).

The cyclizing medium was prepared as follows: 27 g of PPA and 20 g of celite were mixed well with a spatula to form a crumbly mass, then immersed in an oil bath at 120° and stirred vigorously with a mechanical stirrer until the mixture formed fine granules. Then 170 ml of dry toluene and 4.5 g of phosphorus pentoxide were added, and the mixture refluxed with stirring for one hour. This produced a fine sand suspended in toluene.

To this vigorously stirred suspension was added dropwise 7.1 g (0.025 mole) of **4a** in 20 ml of dry toluene. After refluxing for 4 hours, the mixture was cooled and filtered. The solids were washed with toluene, and the combined toluene filtrate and washings were washed with water, then sodium bicarbonate solution, then water, and dried (magnesium sulfate). The bicarbonate wash was saved (see **11a** below). Evaporation of the toluene gave 5.6 g (84%) of **5a** as an oil. The analytical sample was purified over a silica gel column (eluted with ether/hexane/petroleum ether, 2:2:1, saturated with water): ir (neat), 1725 cm^{-1} (ester CO); nmr (deuteriochloroform), δ 1.23 (t, 3H, CH_3), 3.77 (s, 2H, CH_2) 3.9 (s, 3H, CH_3) 4.16 (q, 2H, CH_2), 7.28 (d, 1H, H-4), 7.37 (s, 1H, H-2), 7.47 (d, 1H, H-7).

Anal. Calcd. for $C_{13}H_{13}FO_3S$: C, 58.21; H,4.85; S,11.94; F, 7.09; M.W. 268. Found: C, 58.46; H, 4.71; S, 11.92; F, 7.17; M^+ 268.

5-Methoxy-6-fluoro-3-methylbenzo[*b*]thiophene (**10a**).

The first fraction of eluate from the silica gel column (ether/hexane/petroleum ether, 2:2:1, saturated with water) used to purify the crude cyclized **5a** (above) was collected and concentrated. The solid residue (about 400 mg) was recrystallized from methanol to give white crystals of **10a**, mp 69-70.5°; nmr (deuteriochloroform): δ 2.4 (d, 3H, J = 1.0, CH_3) 4.0 (s, 3H, CH_3O), 7.03 (q, 1H, J = 1.0, H-2), 7.18 (d, 1H, H-4), 7.52 (d, 1H, H-7).

Anal. Calcd. for $C_{10}H_9FOS$: c, 61.22; H, 4.59; S, 16.33; F, 9.69; M.W. 196. Found: C, 61.14; H, 4.50; S, 16.20; F, 9.65; M^+ 196.

5-Methoxy-6-fluoro-3-benzo[*b*]thienylacetic Acid (**11a**).

Acidification of the bicarbonate washings (see **5a** above) gave a white precipitate (250 mg, ~ 5%) of the acid, **11a**. It was recrystallized from acetone, mp 178-180°; ir (potassium bromide): 1690 cm^{-1} (acid CO); nmr (deuteriodimethylsulfoxide): δ 3.86 (s, 2H, CH_2), 3.94 (s, 3H, CH_3), 7.48 (d, 1H, H-4), 7.55 (s, 1H, H-2), 7.88 (d, H, H-7).

Anal. Calcd. for $C_{11}H_9FO_3S$: C, 55.00; H, 3.75; S, 13.33; F, 7.92. Found: C, 55.20; H, 3.86; S, 13.48; F, 7.82.

5-Methoxy-6-fluoro-3-benzo[*b*]thienylacetamide (**6a**).

A solution of 5.6 g (0.02 mole) of crude **5a** in 10 ml of methanol was mixed with 10 ml of ethylene glycol, and ammonia was bubbled into the solution for 24 hours. Ice-cold water was added, and the precipitate was collected and recrystallized from methanol (Norite) to give 3.81 g (76%) of **6a** as white crystals melting at 185-187°; ir (potassium bromide): 3400, 3360 (NH), 1650 cm^{-1} (amide CO); nmr (deuteriodimethylsulfoxide): δ 3.67 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 7.0 (broad, 1H, NH), 7.5 (s, 1H, H-2), 7.55 (d, 1H, H-4), 7.87 (d, 1H, H-7).

Anal. Calcd. for $C_{11}H_{10}FNO_2S$: C, 55.23; H, 4.18; N, 5.86; S, 13.39; F, 7.95; M.W. 239. Found: C, 55.03; H, 3.94; N, 5.82; S, 13.42; F. 7.88; M^+ 239.

5-Methoxy-6-fluoro-3-β-aminoethylbenzo[*b*]thiophene Hydrochloride (**7a**).

Following the procedure of Brown [9], a 100 ml 2-necked flask with magnetic stirrer and septum cap was fitted with a 12″ Vigreux column wrapped with heating tape. A distilling head with receiver was placed at the top of the column, and the whole system was maintained in a nitrogen atmosphere. Then 2.39 g (10 mmoles) of amide **6a** was placed in the flask and 5 ml of THF (dried with sodium and benzophenone) was added through the septum. The solution was brought to reflux, and 2 ml (20 mmoles) of borane dimethyl sulfide (10*M* solution, Aldrich) was added dropwise through the septum over a 10 minute period. After refluxing for 4 hours, during which dimethyl sulfide was collected, the flask was cooled to room temperature, and 3 ml of methanol was added dropwise to destroy excess reducing agent. The septum was replaced by a dropping funnel and 15 ml of a 1.08*M* solutionof hydrogen chloride in ether was added. Stirring was continued for 0.5 hour at room temperature, then 0.5 hour at ice-bath temperature, and the white solid collected and washed with ether to give 2.2 (84%) of crude **7a**.

An analytical sample was prepared by dissolving the material in water, filtering through charcoal, basifying with concentrated sodium hydroxide solution and extracting 3 times with ether. The combined ether extracts were washed with water, dried (magnesium sulfate) and concentrated on a Rotovap. The oily residue solidified on cooling below room temperature. It was dissolved in dry ether and 1.08*M* hydrogen chloride in ether added dropwise until precipitation was complete. The white crystalline precipitate of **7a** was recrystallized from a methanol-ether solution to give pure**7a**, melting at 196-198°; nmr (deuterium oxide): δ 3.2 (m, 4H, CH_2), 3.83 (s, 3H, CH_3), 7.03 (d, J-7, 1H, H-4), 7.30 (s, 1H, H-2), 7.42 (d, J = 11, 1H, H-7); ir (potassium bromide): 3460 (-NH_2) 3000-2450 (b, -NH_3^+), 1610 (ArCH) cm^{-1}. The nmr of the crude solid free base, which was not recrystallized, was taken in deuteriochloroform: δ 1.75 (s, 2H, NH_2), 2.94 (distorted t, 4H, CH_2), 3.86 (s, 3H, CH_3), 7.0 (s, 1H, H-2), 7.13 (d, J = 7, 1H, H-4), 7.40 (d, J = 11, 1H, H-7).

Anal. Calcd. for $C_{11}H_{13}FNOS$: C, 50.49; H, 4.97; N, 5.35; S, 12.24; Cl, 13.56; F, 7.27. Found: C, 50.56; H, 5.09; N, 5.24; S, 12.20; Cl, 13.34; F, 7.44.

5-Methoxy-6-fluoro-3-β-acetamidoethylbenzo[*b*]thiophene (**8a**).

A solution of 2.23 g (8.5 mmoles) of crude **7a** was dissolved in 30 ml of warm water, filtered, and then 4.34 g (42.5 mmoles) of acetic anhydride and 3.49 g (42.5 mmoles) of sodium acetate in 10 ml of water added. The cloudy mixture was stirred for 1 hour at room temperature, then poured over ice. The white crystalline solid was collected, washed with water and dried, to give 2.18 g (96%) of crude **8a** melting at 115-118°. Twice recrystallized from ethanol, it melted at 119.5-121°; ir (potassium bromide): 3230 (NH), 1630 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 1.96 (s, 3H, CH_3), 3.0 (t, 2H, CH_2), 3.64 (q, 2H, CH_2), 3.95 (s, 3H, CH_3), 5.85 (br, 1H, NH), 7.03 (s, 1H, H-2), 7.32 (d, J = 7, 1H, H-4), 7.45 (d, J = 11, 1H, H-7).

Anal. Calcd. for $C_{13}H_{14}FNO_2S$: C, 58.43; H, 5.24; N, 5.24; S, 11.99; F, 7.12; M.W. 267. Found: C, 58.70; H, 5.30; N, 5.26; S, 12.15; F, 6.94; M^+ 267.

3-Chloro-4-methoxyphenylisothiocyanate (**2b**).

A mixture of 475 ml of glacial acetic acid and 25 ml of acetic anhydride was refluxed overnight, then cooled in an ice-bath till crystals of acetic acid formed (16-17°). Then 10.64 g (0.15 mole) of dry chlorine gas was added. Lead thiocyanate (24.25 g, 0.075 mole) was then added with stirring. Finally 14.26 g (0.10 mole) of *o*-choroanisole (**1b**) (Aldrich) was added, and stirring was continued for 4 hours at room temperature. The solution was then filtered to remove lead chloride, and the filtrate poured into 2 liters of ice-water. The crystalline precipitate was collected and washed with cold water, and air-dried. The yellow solid was dissolved in ether, filtered to remove insoluble solids, and concentrated to give 19.3 g (97%) of lemon-yellow needles melting at 38-39.5°. An analytical sample of **2b**, recrystallized from carbon tetrachloride hexane/mixture, melted at 38.5-39.5°; ir (potassium bromide): 2160 cm^{-1} (CN); nmr (deuteriochloroform): δ 3.95 (s, 3H, CH_3), 6.98 (d, J = 8, 1H, H-5), 7.49 (dd, J (*ortho*) = 8, J (*meta*) = 2, 1H, H-6), 7.65 (d, J = 2, 1H, H-2).

Anal. Calcd. for C_8H_6ClNOS: C, 48.13; H, 3.00; N, 7.02; Cl, 17.77; S, 16.04. Found: C, 47.92; H, 2.93; N, 6.82; Cl, 17.56; S, 16.04.

3-Chloro-4-methoxybenzenethiol (**3b**).

A solution of 26.5 g (0.133 mole) of **2b** in 130 ml of ether was added dropwise to 7.0 g (0.18 mole) of lithium aluminum hydride suspended in 500 ml of dry ether. The mixture was then refluxed for 2 hours, and quenched by dropwise addition of water, then 6*N* hydrochloric acid until inorganic salts were dissolved. The aqueous layer was separated, and extracted twice with ether. The combined ether extracts were washed twice with water and dried (magnesium sulfate). Evaporation of the ether left an oil which solidified on cooling, and was recrystallized from hexane to give 22.1 g (96%) of pure **3b**, melting at 42.5-43.5°; ir (potassium brom-

ide) 2590 cm^{-1} (SH); nmr (deuteriochloroform): δ 3.41 (s, 1H, SH), 3.76 (s, 3H, CH_3), 6.69 (d, 1H, H-5), 7.07 (m, 1H, H-6), 7.24 (d, 1H, H-2).

Anal. Calcd. for C_7H_7ClOS: C, 48.15; H, 4.01; S, 18.34; Cl, 20.32. Found: C, 48.10; H, 3.97; S, 18.42; Cl 20.33.

Ethyl 4-(3'-Chloro-4'-methoxyphenylthio)acetoacetate (**4b**).

Dropwise addition of 22.2 g (0.135 mole) of ethyl 4-chloroacetoacetate (Aldrich) to a solution of 22.6 g (0.13 mole) of **3b** and 60 ml of pyridine in 90 ml of dry ether with stirring, followed by 2 hours of reflux, gave a mixture containing a precipitate of pyridine hydrochloride. Water (100 ml) was added, and the water layer separated, and washed twice with ether. The combined ether extracts were washed with water, then 3*N* hydrochloric acid and finally dilute sodium bicarbonate solution, then dried (magnesium sulfate). Concentration gave 39.2 g (100%) of an oil which was used in the next step without further purification. An analytical sample of **4b** was purified through a silica gel column; ir (neat): 1760 (ester CO), 1720 (ketone CO), 1660, 1630 cm^{-1} (enol C=C); nmr (deuteriochloroform): δ 1.24 (t, 3H, CH_3), 3.61 (s, 2H, CH_2), 3.68 (s, 2H, CH_2), 4.16 (q, 2H, CH_2), 6.84 (d, 1H, H-5), 7.28 (q, 1H, H-6), 7.40 (d, 1H, H-2).

Anal. Calcd. for $C_{13}H_{15}ClO_4S$: C, 51.58; H, 4.96; S, 10.58; Cl, 11.72. Found: C, 51.86; H, 5.16; S, 10.93; Cl, 11.54

Cyclization of **4b**.

The cyclizing medium was prepared from 60 g of celite, 80 g of PPA and 10 g of phosphorus pentoxide in 360 ml of toluene, as described above (see **5a**). To this vigorously stirred suspension was added 14.64 g (0.048 mole) of crude **4b** in 40 ml of toluene, and the mixture refluxed for 24 hours (intermittant monitoring by tlc after 4 hours showed **4b** still present, in trace amounts even at 24 hours). The mixture was then cooled and filtered, and the solid residue washed with toluene. The combined filtrate and toluene washings were washed with water, then sodium bicarbonate solution (see **11b**, below), then dried over magnesium sulfate. Evaporation of the toluene gave 11.1 g (81%) of a crude oil consisting of several components. It was separated by column chromatography, as described below.

5-Methoxy-6-chloro-3-benzo[*b*]thienylacetic acid (**11b**).

The sodium bicarbonate washings of the toluene reaction medium (above) were acidified with phosphoric acid, and extracted with ether several times. After concentrating the ether solution, trace amounts of a white crystalline solid, melting at 176-179°, were obtained. These proved to be the acid **11b**, which was prepared unequivocally from ester **5b** by hydrolysis in dilute sodium hydroxide solution. After acidification, the white precipitate was dried and recrystallized from acetone/hexane mixture to give **11b**, melting at 178-180°; ir (potassium bromide): 2500-3000 (COOH), 1700 cm^{-1} (CO); nmr (deuteriodimethylsulfoxide): δ 3.88 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 7.43 (s, 1H, H-4), 7.58 (s, 1H, H-2), 8.08 (s, 1H, H-7).

Anal. Calcd. for $C_{11}H_9ClO_3S$; C, 51.47; H, 3.51; S, 12.48; Cl, 13.82. Found: C, 51.26; H, 3.49; S, 12.63; Cl, 13.66.

5-Methoxy-6-chloro-3-methylbenzo[*b*]thiophene (**10b**).

A column of 200 g of 60-230 mesh silica gel was treated with a solvent system of 2 parts of ether, 2 parts of hexane, and 1 part of petroleum ether, saturated with water. Then 13 g of the crude cyclization product (see above) was dissolved in the solvent mixture and passed through the column, using about 1200 ml of solvent.

The first fraction, about 200 ml, contained nearly pure **10b**. Evaporation of the solvent gave 0.5 g (5%) of crystals, which after three recrystallizations from ethanol melted at 106-107°: nmr (deuteriochloroform): δ 2.4 (d, J = 1.0, 3H, CH_3), 3.97 (s, 3H, CH_3), 7.03 (q, J = 1.0, 1H, H-2), 7.10 (s, 1H, H-4), (s, 1H, H-7).

Anal. Calcd. for $C_{10}H_9ClOS$: C, 56.48; H, 4.24; S, 15.06; Cl, 16.69; M.W. 212. Found: C, 56.27; H, 4.09; S, 14.99; Cl, 16.49; M^+ 212.

Ethyl 5-Methoxy-6-chloro-3-benzo[*b*]thienylacetate (**5b**).

After about 100 ml of solvent was collected as fraction 2, containing a mixture of substances (**5b** and **10b**), about 300 ml of solvent was collected as fraction 3. After concentration of the solvent to about one-half volume, the solution was stored in a refrigerator overnight. White crystals (7.0 g, 52%) of **5b**, melting at 38-45°, were collected. Two further passes through silica gel did not improve the melting point appreciably. The nmr (deuteriochloroform) of this material, which analyzed well, showed about 10% of the isomer **12**, as follows: δ 1.22 (t, 3H, CH_3), 3.76 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 4.16 (q, 2H, CH_2), 6.9 (d, J = 9, 0.1 H, H-6), 7.18 (s, 0.9 H, H-4), 7.30 (s, 1H, H-2), 7.55 (d, J = 9, 0.1 H, H-7), 7.70 (s, 0.9 H, H-7).

Anal. Calcd. for $C_{13}H_{13}ClO_3S$: C, 54.84; H, 4.57; S, 11.25; Cl, 12.46; M.W. 284. Found: C, 55.06; H, 4.32; S, 11.02; Cl, 12.31; M^+ 284.

p-(4-Chloro-5-methoxy-3-benzo[*b*]thienylacetyl)toluene (**13**).

A final 500 ml fraction of eluant was concentrated to 100 ml and cooled in an ice-bath, to give about 0.3 g (2.5%) of fine white crystals melting at 140-145°. One recrystallization from ethanol gave crystals melting at 149-151°; ir (potassium bromide): 3100, 3050 (ArH), 1650 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.43 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 4.83 (s, 2H, CH_2), 7.07 (d, J = 9, 1H, H-6), 7.28 (s, 1H, H-2), 7.30 (d, J = 8, 2H, H-b), 7.72 (d, J = 9, 1H, H-7), 8.0 (d, J = 8, 2H, H-c).

Anal. Calcd. for $C_{18}H_{15}ClO_2S$: C, 65.36; H, 4.54; S, 9.68; Cl, 10.73; M.W. 330. Found: C, 65.09; H, 4.60; S, 10.00; Cl, 10.70; M^+ 330.

5-Methoxy-6-chloro-3-benzo[*b*]thienylacetamide (**6b**).

A. From Purified Ester **5b**.

The ester **5b**, purified by three passes through the column (above) was used in this preparation. A mixture of 2.84 g (0.01 mole) of **5b** and 25 ml of ethylene glycol in 25 ml of ethanol was saturated with ammonia, and stirred overnight at room temperature. It was then diluted with ice-water, and the white precipitate collected, washed with water, then ether, and dried, to give 2.17 g (85%) of **6b**, melting at 191-193°. The analytical sample, recrystallized from methanol, melted at 193-194.5°; ir (potassium bromide): 3450, 3340, 3220 (NH), 3080 (ArH), 1690 cm^{-1} (CO); nmr (deuteriodimethylsulfoxide): δ 3.67 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 7.0 (broad, 2H, NH_2), 7.48 (s, 1H, H-4), 7.51 (s, 1H, H-2), 7.99 (s, 1H, H-7).

Anal. Calcd.for $C_{11}H_{10}ClNO_2S$: C, 51.67; H, 3.91; N, 5.48; S, 12.53; Cl, 13.86. Found: C, 51.48; H, 4.01; N, 5.55; S, 12.45; Cl, 13.69.

B. From Crude Cyclization Product.

The crude ester, described above, was used in this preparation. Treatment of 2.84 g (0.01 mole) of this crude **5b** as above gave 1.66 g (65%) of off-white solid melting at 190-194°. Two recrystallization from methanol gave **6b**, identical to that prepared from the pure ester.

5-Methoxy-4-chloro-3-benzo[*b*]thienylacetamide (**14**).

The methanol mother liquors from five preparations described under B above were combined and evaporated to give a solid melting at 170-174°. After several washings with acetone and chloroform, the residue was recrystallized several times from ethanol to give 0.5 g of white crystals melting at 212-214°; ir (potassium bromide): 3420, 3330, 3220, 3120 (NH), 3080 (ArH), 1660 cm^{-1} (CO); nmr (deuteriodimethylsulfoxide): δ 3.9 (s, 5H, CH_3 and CH_2), 7.0 (br, 2H, NH_2), 7.28 (d, J = 9, 1H, H-6), 7.37 (s, 1H, H-2), 7.9 (d, J = 9, 1H, H-7).

Anal. Calcd. for $C_{11}H_{10}ClNO_2S$: C, 51.67; H, 3.91; S, 12.53; M.W. 255. Found: C, 51.55; H, 3.98; S, 12.40; M^+-$CONH_2$=211.

5-Methoxy-6-chloro-3-β-aminoethylbenzo[*b*]thiophene Hydrochloride (**7b**).

A solution of 2.55 g (10 mmoles) of **6b** in 5 ml of THF was reduced with 7.5 ml of 2.0 molar borane/dimethyl sulfide (Aldrich) using the method previously described for compound **7a**. After 4 hours reflux, the mixture was cooled to room temperature, and 15 ml of 1.4*M* hydrogen chloride in methanol was added dropwise. After the vigorous evolution of hydrogen had subsided, the solution was heated to reflux for 3 hours, allowing the methyl borate and methanol to distill. After cooling, dry ether was added, and the white precipitate collected, washed with ether and dried to give 2.25 g (81%) of crude hydrochloride **7b**. A sample recrystallized from

methanol/ether mixture melted at 242-245°, and did not depress the melting point of an authentic sample [2]. The nmr spectrum of this sample was identical to that previously reported.

5-Methoxy-6-chloro-3-β-acetamidoethylbenzo[*b*]thiophene (**8b**).

Solution of 3.0 g (10.8 mmoles) of crude **7b** in warm water (100 ml) left 0.3 g of insoluble impurities (after drying) which were removed by filtration. Then 5.1 g (50 mmoles) of acetic anhydride and 4.1 g (50 mmoles) of sodium acetate dissolved in 15 ml of water were added. The mixture was stirred for 1.0 hour at room temperature and poured over ice. The white precipitate was collected, washed with water, dried and recrystallized from ethanol, to give 2.45 g (82%) of **8b**, melting at 142-144°, which did not depress the melting point of an authentic sample [2]. The nmr spectrum of this sample was identical to that previously reported.

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[12] We are indebted to Dr. H. K. Kim, of the Center for Population Research, Contraceptive Development Branch, for the Drug Evaluation Reports summarized in Tables I and II.

[13] It was found that the use of 1.5 equivalents of thiocyanogen chloride gave a much improved yield of **2b** in this reaction, and it is likely that the yield of **2a** could be improved by this modification of the procedure.